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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/596,062	LIU ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7 and 19-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 19-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the reply of October 16, 2009. Applicant's arguments and amendments to the claims have been fully considered but are not persuasive to place all claims in condition for allowance. All rejections not reiterated herein are hereby withdrawn. In particular, the objection to the specification has been obviated by the amendment to the specification. The rejection of claim 7 under 35 U.S.C. 112, second paragraph has been obviated by the amendment to claim 7.

2. Claims 7 and 19-26 are pending and have been examined herein.

Sequence Listing

3. The CRF and paper copies of the Sequence Listing filed on October 16, 2009 have been entered.

The following are new grounds of rejection necessitated by Applicant's amendments to the claims:

Claim Rejections - 35 USC § 112 second paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22-26 are indefinite over the recitation of $CD24^{1580TG}$. This phrase is not clearly defined in the specification and there is no art recognized definition for this phrase. The specification in Examples 6 and 7 and in Figure 6 refers to a SNP at

position 1580 and recites the term "TG." Originally filed claim 7 refers to a deletion of nucleotides at positions 1580 and 1581 of the native CD24 cDNA of SEQ ID NO: 1. However, the specification and prior art do not define or otherwise characterize $CD24^{1580TG}$. Accordingly, it is unclear as to what is intended to be encompassed by $CD24^{1580TG}$.

Claim Rejections - 35 USC § 112 first paragraph – New Matter

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7 and 19-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The specification as originally filed does not provide support for the amendment to claims 7 and 19-21 to recite a method wherein deletions at positions 1580 and 1581 in at least one allele of the CD24 gene indicates that an individual has a lesser likelihood of experiencing rapid progression of multiple sclerosis as compared to an individual having two alleles of the CD24 gene having a TG at positions 1580 and 1581. Originally filed claim 7 recited a method wherein deletions at positions 1580 and 1581 in at least one allele of the CD24 gene indicates that an individual has a greater likelihood of experiencing rapid progression of multiple sclerosis as compared to an individual

having two alleles of the CD24 gene having a TG at positions 1580 and 1581. Accordingly, originally filed claim 7 does not provide support for this amendment since the interpretation of the presence of the deletion of nucleotides 1580 and 1581 was opposite of that recited in amended claims 7 and 19-21. The response points to paragraphs [0113-0115] and Figure 6 as providing support for this amendment. However, para [0113-0115] provide the results of a study that is limited to the deletion of nucleotide 1580 of the CD24 gene. In particular, para [0114] states "Survival analysis revealed that SNP at 1580 have significant impact for the progression of MS. As shown in Fig. 6, the genotypes at this position associate with the time span from the day of first MS-like symptom to the day when the patients requires walking aid." Figure 6 refers to "P1580" and compares a deletion to a "TG." Figure 6 depicts a plot of the proportion surviving versus survival time in years. Accordingly, the cited portions of the specification do not in fact address a correlation between the presence of a deletion of both nucleotides 1580 and 1581 and a lesser likelihood of rapid progression of MS.

The specification as originally filed also does not provide support for the recitation in newly added claims 22-26 that an individual having a has a lesser likelihood of experiencing rapid progression of multiple sclerosis than a human individual with MS who is homozygous for the $CD24^{1580TG}$ allele. The specification does not specifically disclose a $CD24^{1580TG}$ allele and it is not clear as to what is intended to be encompassed by this allele. Thereby, the specification does not provide support for the concept of comparing the likelihood of rapid progression of MS in an individual homozygous or heterozygous for the deletion of nucleotide 1580 in the CD24 gene with

an individual who is homozygous for a $CD24^{1580TG}$ allele. Figure 6 and Tables 2 and 3 use the nomenclature "TG" but do not define what is encompassed by an individual with a "TG." Further, while Figure 6 depicts a plot of the proportion surviving versus survival time in years and includes data for individuals denoted as "TG/TG," "TG/del," and "del/del," Figure 6 does not provide support for the distinct concept of the likelihood that an individual will have a more rapid progression of MS. Note that the concept of rapid progression of MS is considered to be distinct from the concept of survival time in years for subjects having MS. While para [0114] states "Survival analysis revealed that SNP at 1580 have significant impact for the progression of MS," this statement does not clarify whether individuals with the deletion of nucleotide 1580 have an increased or decreased likelihood of progression of MS. Also, while para [0114] states "As shown in Fig. 6, the genotypes at this position associate with the time span from the day of first MS-like symptom to the day when the patients requires walking aid," Figure 6 does not in fact include any information regarding time span to the day a patient requires a walking aid and the statement at para [0114] does not clarify which particular genotypes are correlated with shorter or longer time spans to the day a patient requires a walking aid.

6. The following rejection was previously presented in the Office Action of July 17, 2009 and has been modified herein to address the amendments to the claims.

Claim Rejections - 35 USC § 112 first paragraph - Enablement

7. Claims 7 and 19-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

Claims 7 and 19-21 are drawn to a method for predicting the likelihood that a human individual who has been diagnosed with multiple sclerosis (MS) will experience rapid progress of MS comprising determining if there is a deletion at positions 1580 and 1581 of the CD24 gene in the individual, wherein deletions of TG at positions 1580 and 1581 indicate that the individual has a lesser likelihood of experiencing rapid progression of MS than an individual diagnosed with MS and having two alleles with a TG at positions and 1581.

Newly added claims 22-26 are drawn to a method for predicting the likelihood that a human individual who has been diagnosed with multiple sclerosis (MS) will experience rapid progress of MS comprising determining if there is a deletion at position 1580 of the CD24 gene in the individual, wherein an individual homozygous or

heterozygous for a deletion at position 1580 of the CD24 gene has a lesser likelihood of experiencing rapid progression of multiple sclerosis than a human individual with MS who is homozygous for the $CD24^{1580TG}$ allele. The specification and claims do not clearly define what constitutes a $CD24^{1580TG}$ allele.

Newly added claim 23 further recites analyzing the sample to determine if the human individual's CD24 gene includes a $CD24^{1580del}$ allele using cell surface expression of the CD24 gene.

Nature of the Invention

The claims encompass methods for predicting the likelihood that an individual who has been diagnosed with MS will experience rapid progress of MS by assaying for a deletion at positions 1580 and 1581 of the CD24 gene. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches the occurrence of a deletion of nucleotides T and G at positions 1580 and 1581, relative to present SEQ ID NO: 1. The deletion occurs in the 3' untranslated region of the CD24 gene (page 38).

The specification provides the results of a genotyping study of the CD24 gene in 8 normal human subjects. As set forth in Table 2 (page 38), a deletion at position 1580 appears to have been detected in at least one allele of 3 of the normal subjects.

The specification also provides the results of a genotyping study of the CD24 gene in 241 control and 221 MS patients. The genotyping study screened for the following polymorphisms: 226C/T, 1110A/G, 1580 and 1581 TG deletion, and 1678A/G (page 39). The specification reports that the 1110G allele showed the strongest association with MS and that the significance of the other SNPs requires further testing (see para [0109] and Table 3).

The specification also provides the results of a study to screen for a correlation between the "Polymorphism at position 1580 and MS progression" (Example 7, page 40). The results are presented in Figure 6. Therein, the proportion surviving versus survival time in years is provided relative to individuals with the deletion at both alleles. The figure includes the annotation that: TG/TG vs. TG/del p=0.016, TG/TG vs del/del p=0.059, and TG/del vs del/del p=0.177. Since a p value greater than 0.05 is generally not considered to be statistically significant, Figure 6 appears to indicate only that individuals heterozygous for the deletion as compared to subjects homozygous for alleles lacking the deletion are correlated with longer survival. The specification does not provide any explanation as to why individuals heterozygous for the 1580 deletion show a correlation with survival, whereas individuals homozygous for the 1580 deletion do not show a correlation with survival, and individuals homozygous for the allele without a deletion also do not show a correlation with survival.

It is noted that the originally filed claim 7 recited that an individual having a deletion of TG at positions 1580 and 1581 has a greater likelihood of experiencing rapid progression of MS than an individual having TG at positions 1580 and 1581. It is also

noted that the specification (para [010]) states that "As used herein in reference to MS, the term "rapid progression" means that an individual has reached or will reach EDSS 6.0 in a shorter time period than average from the time of first diagnosis of MS." However, the data provided in the specification appears to be limited to survival time and not to the time period that occurred before an individual reaches EDSS 6.0.

It is also noted that claim 7 (and dependent claims 19-21) have now been amended to recite that having a deletion of TG at positions 1580 and 1581 has a lesser likelihood of experiencing rapid progression of MS than an individual having TG at positions 1580 and 1581. However, the results provided in Figure 6 are with respect to the distinct concept of a deletion of nucleotide 1580. The specification does not appear to specifically provide any data for methods which detect a deletion at both nucleotide positions 1580 and 1581. That is, Figure 6 refers to “P1580” and para [0113] and [0114] refer to the polymorphism at position 1580. The specification does not provide any guidance as to the relationship between individuals having a deletion at nucleotide 1580 and individuals having a deletion of both nucleotides 1580 and 1581. Also, the specification does not clearly define what is intended to be encompassed by subjects identified as having “TG,” as is recited in Tables 2 and 3 and Figure 6.

Further, in the post-filing date reference of Wang et al (The Journal of Immunology. 2007. 178: 129.1), of which the present inventors are co-authors, it appears that conflicting results were reported. Wang teaches that in a study of 316 MS patients and 342 controls, the 1580-1581 dinucleotide deletion was associated with

significantly reduced risk of MS and delayed progression of MS. Note that this finding is in opposition to that which was claimed in original claim 7.

Similarly, in the reference of Wang et al (PLoS Genetics. April 2007. 3: e49, 0508-0517), of which the present inventors are also co-authors, it is reported that the 1580-1581 dinucleotide deletion (referred to therein as $P1527^{del}$) is preferentially transmitted to unaffected individuals (page 0513, col. 2). Wang also teaches the results of a study that compared the proportion of survivors and years from first symptom for subjects having the del/del, del/GT and GT/GT genotypes (Figure 3 and page 0511). Wang reported that MS patients with the TG/del or del/del genotype had a more delayed disease progression as compared to MS patients with the TG/TG genotype.

On the other hand, Gonzalez (Neurology. March 2009. 72 (supplement 3), A376, abstract P08.040) studied the association between the CD24 1580-1581 dinucleotide deletion (referred to therein as the P1527 TG/del polymorphism) and protection against MS in a population from Argentina. Gonzalez found that there was no difference between the frequency of the mutation in subjects with MS as compared to controls and concluded that the deletion did not provide a protective effect against MS in the study population from Argentina.

The Predictability or Unpredictability of the Art :

The art of determining an association between a genotype and a phenotype, such as progression of MS, are highly unpredictable. Knowledge that the polymorphism is present in a subject having a phenotype does not permit one to predictably determine

whether that polymorphism will be reproducibly associated with the phenotype. In particular, in the present situation, the information presented in the specification is not sufficient to permit one to ascertain whether deletion of nucleotides 1580 and 158, or 1580 alone, in one or both CD24 alleles is correlated with rapid progression of MS. The data provided in the specification is not in fact directed to the study of the rate of progression of MS. Rather, the results presented in the present specification are limited to the analysis of survival time of patients with MS. Further, the results in Figure 6 are not statistically significant for the comparison of individuals homozygous for the deletion versus homozygous for the absence of the deletion ($p = 0.059$) or for individuals homozygous for the deletion versus individuals having one allele with the GT ($p=0.177$). Also, the conclusion provided in original claim 7 conflicts with the teachings of the present inventors in their post filing date reference in that original claim 7 required that a deletion of TG at positions 1580-1581 is correlated with increased likelihood of rapid progression of MS, whereas the Wang et al references cited above teach that a deletion of TG at positions 1580-1581 is correlated with a more delayed progression of MS. Yet, there is no specific data in the specification as originally filed to establish that a deletion of both nucleotides 1580 and 1581 is correlated with an increased likelihood of progression of MS in subjects having MS as compared to human individuals homozygous for a TG at positions 1580 and 1581. There is also no specific data provided in the specification to establish that a deletion of nucleotide 1580 is correlated with an increased likelihood of progression of MS in subjects having MS as compared to human individuals homozygous for a $CD24^{1580del}$ allele.

Further, the art is replete with evidence that gene association studies are frequently wrong. In fact, Lucentini et al (The Scientist (2004) Vol 18, page 20) titled his article "Gene Association Studies Typically Wrong" and teaches therein that reproducible association studies are “few and far between.” The reference reports that “when a finding is first published linking a given gene with a complex disease, there is only roughly a one third chance that studies will reliably confirm the finding. When they do, they usually find the link is weaker than initially estimated. The first finding is usually ‘spurious, or it is true, but it happens to be really exaggerated, ’ …there may be no way to predict which new gene-association studies will be verified with multiple replication.” This is consistent with the teaching of Wacholder et al (J. Natl. Cancer Institute (2004) 96(6):434-442) who notes that "Too many reports of associations between genetic variants and common cancer sites and other complex diseases are false positives (see abstract). Ioannidis et al. (Nature genetics (2001) 29:306-309) further supports this conclusion in pointing out the heterogeneity of results among different studies of genetic polymorphisms (see abstract, for example).

The teachings in the specification support the unpredictability in the art in determining an association between a polymorphism in the CD24 gene and a phenotype, such as MS. In particular, the specification teaches that the CD24 1678A/G mutation was not correlated with MS (see page 39).

The post-filing date art also supports the unpredictability in the art of determining an association between CD24 polymorphisms and MS. Specifically, Goris (2006) teaches the results of a study of the frequency of the CD24 Ala/Val polymorphism in

1180 MS patients and 1168 controls from Belgium and the UK. Goris states that "We did not observe the previously reported overrepresentation of the T/T ($CD24^{v/v}$) genotype among MS patients in either of the study populations, nor in combined analysis. Indeed, there was a trend in the opposite direction, with an under-representation of the T allele in cases, in the UK population" (pages 201-202). Goris also did not find an association between this polymorphism and MS disease progression (page 202).

Further, newly added claim 23 requires detecting the deletion of nucleotide 1580 of the CD24 gene by assaying for cell surface expression of the CD24 protein. However, it is highly unpredictable as to whether a deletion of one nucleotide in the 3' UTR of the CD24 gene will effect protein expression levels, such that a change in cell surface expression of CD24 can be detected as specifically indicative of the 1580 nucleotide deletion. The specification (para [045]) teaches that CD24 is a GPI anchored molecule and that cleavage of the C-terminal end is required prior to GPI attachment. It is stated that an ala/val polymorphism at amino acid position 226 of the CD24 protein may alter the efficiency of cleavage. The specification (page 20) reports that "As shown in Table 1 (Exp. 2) and Fig. 4c, although the $CD24^{226a/v}$ T cells expressed higher CD24 than the $CD24^{226a/a}$ T cells, the increase is less than 2-fold. The small increase may explain why the $CD24^{226a/v}$ genotype had no measurable effect on the risk and progression of MS." Accordingly, the specification teaches that even with the $CD24^{226a/v}$ genotype, detection of this genotype is not predictive of progression of MS. Since the specification has not established that a deletion of nucleotide 1580 effects cell surface

expression of CD24, it is further highly unpredictable as to whether a change in the level of cell surface expression of CD24 can be detected as indicative of the presence of the deletion of nucleotide 1580 in the 3' UTR, and thereby as indicative of the decreased likelihood of more rapid progression of MS.

Amount of Direction or Guidance Provided by the Specification and Degree of Experimentation:

The specification does not provide sufficient guidance as to how to practice a method of predicting the likelihood of rapid progression of MS in subjects having MS by assaying for deletion of both nucleotides 1580 and 1581 or by assaying for a deletion of only nucleotide 1580. The data provided in the specification is limited to methods in which survival time in years is measured. There is no specific data provided in the specification which addresses the progression of MS. Moreover, the specification does not appear to specifically provide any data for subjects having a deletion of both nucleotides 1580 and 1581, since the specification appears to only address subjects having a deletion of nucleotide 1580 (see para [0113-0114] and Figure 6). Moreover, the specification does not clearly define what constitutes an individual with a TG, as is recited in Tables 2 and 3 and Figure 6, or what constitutes an individual having a $CD24^{1580TG}$ allele. In view of the unpredictability in the art and the lack of specific guidance provided in the specification and in view of the lack of any teachings regarding a functional effect of the deletion of nucleotide 1580 or the deletion of nucleotides 1580 and 1581 in the CD24 gene, extensive experimentation would be required to practice the invention as it is broadly claimed.

Further, regarding claim 23, the specification does not provide any guidance as to how to detect the deletion of nucleotide 1580 of the CD24 gene by assaying for cell surface expression of the CD24 protein. As discussed above, the specification has not established that a deletion of nucleotide 1580 effects the cell surface expression of the CD24 protein. It is not readily apparent that a deletion of one nucleotide in the 3' UTR of the CD24 gene would be expected to effect cleavage of the CD24 protein and/or cell surface protein expression levels, such that a change in cell surface expression of CD24 could be detected as specifically indicative of the deletion of nucleotide 1580 in the CD24 gene. The specification does not provide any examples or other type of guidance as to how to detect the deletion of nucleotide 1580 in the 3' UTR of the CD24 gene by assaying for cell surface expression of the CD24 protein.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of

one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, as discussed above, there is a high level of unpredictability in the art of determining an association between polymorphisms in the CD24 gene and rapid progression of MS. For the reasons set forth above, the teachings in the specification do not appear to establish the correlation required by the present claims that the presence of a deletion of nucleotides 1580-1581 (with respect to SEQ ID NO: 1) in one or both alleles of the CD24 gene is associated with lesser likelihood of rapid progression of MS as compared to subjects homozygous for a TG at nucleotides 1580-1581 of the CD24 gene, or a correlation that deletion of nucleotide 1580 in the CD24 gene is associated with a lesser likelihood of rapid progression of MS as compared to individuals homozygous for a $CD24^{1580TG}$ allele. Additionally, the specification does not provide guidance to practice a method of detecting the deletion of nucleotide 1580 by assaying for cell surface expression of the CD24 gene.

In view of the breadth of the claims, the unpredictability in the art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, and the negative teachings in the art balanced only against the high skill level in the art, undue experimentation would be required to practice the claimed invention.

Response to Remarks:

In the response filed October 16, 2009, Applicants traversed this rejection. Those arguments as they pertain to the claims as amended are addressed below. It is noted

that the prior rejection as it concerned methods of predicting rapid progression of MS in non-human subjects has been obviated by the amendment to the claims to limit the claims to methods for predicting the likelihood that a human individual will experience rapid progression of MS.

The response states that Applicants have provided support for obtaining a sample of genetic material and assaying for a deletion at positions 1580 and 1581 of the CD24 gene. Applicants thereby conclude that the specification has enabled the claimed methods.

These arguments have been fully considered but are not persuasive because teaching methods for obtaining genetic samples and assaying for a deletion of nucleotides 1580 and 1581 is not sufficient to establish enablement for the claimed method which predicts the likelihood that a human individual will experience rapid progression of MS by assaying for a deletion of nucleotide 1580 or nucleotides 1580 and 1581 in the CD24 gene. The claimed methods require that there is a correlation between the deletion of nucleotide 1580 or a deletion of both nucleotides 1580 and 1581 and risk of rapid progression of MS. However, the specification has not established such a correlation.

The response states that the specification describes in detail how to use cell surface expression of CD24 to carry out the claimed method. However, a general statement in the specification at para [049] that a polymorphism can be detected by assaying for cell surface expression of CD24 is not considered to constitute a “detailed” and enabling description of how to detect the particular polymorphism of a deletion of

nucleotide 1580 by assaying for cell surface expression of CD24. In fact, the specification details methods for trying to determine if there is a correlation between the presence of an Ala/Val polymorphism at position 226 of the CD24 protein and cell surface expression of the CD24 protein. While the polymorphism at position 226 of the CD24 protein effected cell surface expression levels to a small degree (approximately 2-fold), the specification reports that the Ala/Val polymorphism at position 226 of the CD24 protein was NOT correlated with progression of MS (see page 20). With respect to the elected polymorphism, the specification does not provide any information regarding the functional effect of a deletion of nucleotide 1580 in the 3' UTR of the CD24 gene and cell surface expression levels of the CD24 protein. The specification does not provide sufficient guidance to enable methods for specifically detecting the deletion of nucleotide 1580 by assaying for the cell surface expression of the CD24 protein, such that a change in the level of cell surface expression of the CD24 protein, or the presence of cell surface expression of the CD24 protein would be indicative of the occurrence of a deletion of nucleotide 1580 of the CD24 gene, which would thereby be indicative of a lesser likelihood of progression of MS.

The response states that “Applicants have amended the claims, which were inadvertently drafted to recite a greater rather than lesser likelihood of rapid progression of MS. Support for the amended claim, in which and individual with deletions at positions 1580 and 1581 in at least one allele of the individual's CD24 gene has a lesser likelihood of experiencing rapid progression of multiple sclerosis, can be found in Figure 6, which the Examiner has indicated shows a correlation between subjects homozygous

for the deletion with longer survival." However, for the reasons discussed in detail above, the specification as originally filed does not provide support for this embodiment. It is noted that claims 7 and 19-21 have been amended to recite a correlation that is opposite that recited in original claim 7. Further, the data in the originally filed specification appears to be limited to deletion of only nucleotide 1580, rather than a deletion of both nucleotides 1580 and 1581. Also, the results obtained in individuals having a deletion of nucleotide 1580 was made in comparison to individuals having a "TG." Yet, the specification does not clearly define what constitutes an individual having a "TG." That is, the specification does not clearly indicate that a TG refers to the presence of a TG at nucleotide positions 1580 and 1581. The specification also does not define what constitutes a $CD24^{1580TG}$, as is recited in claims 22-26. Moreover, the findings presented in Figure 6 are limited to an analysis of the survival time of the subjects having MS. No information was provided in Figure 6 or elsewhere in the specification as originally filed regarding progression of MS.

The response states that the findings of Gonzalez related to a different problem than that evaluated by Wang et al and the present invention. It is stated that Gonzales analyzed the frequency of the P1527 (TG deletion) in subjects having MS as compared to subjects that do not have MS, whereas the present claims are concerned with a correlation between the polymorphism and progression of MS.

These arguments have been fully considered but are not persuasive. While Gonzalez does not address the correlation between the P1527 (TG deletion) and progression of MS, the findings of Gonzalez do support the unpredictability in the art of

establishing a correlation between a polymorphism in the CD24 gene and a MS phenotype. Note that Gonzalez states that "The results of this study are different from [those] published previously because we did not find differences between patients and controls," indicating that the findings regarding an association between the CD24 polymorphism and MS are not reproducible.

Applicants point to Example 7 as stating that "Survival analysis revealed that SNP at 1580 have a significant impact for the progression of MS." Applicants also point to the statement "As shown in Fig. 6, the genotypes at this position associate with the time span from the day of first MS-like symptoms to the day when the patients require walking aid." It is asserted that requiring walking aid essentially defines stage EDSS 6.0 of multiple sclerosis. Applicants conclude that the data provided in the specification fully support the claim for an individual that is homozygous or heterozygous for the $CD24^{1580del}$ allele (or the corresponding deletions at positions 1580 and 1581) having a lesser likelihood of experiencing rapid progression of multiple sclerosis.

These arguments have been fully considered but are not persuasive. The specification does not accurately characterize the results provided in Figure 6. Figure 6 does not provide any information regarding time span from the day of first MS-like symptoms to the day the patient requires a walking aid. Rather, Figure 6 is a plot comparing the proportion surviving versus survival time in years. Thereby, Figure 6 cannot be relied upon as establishing a correlation between the deletion of nucleotide 1580 and time to when a patient requires a walking aid, and thus progression of MS. There is no additional information provided elsewhere in the specification regarding an

association between particular 1580 genotypes and the time span from the first MS-like symptoms to the time at which a patient required a walking aid. Further, the general statement at para [0114] that "Survival analysis revealed that SNP at 1580 have a significant impact for the progression of MS" is not sufficient to enable the claimed invention because this statement does not indicate which 1580 genotype (a deletion of this nucleotide or the presence of this nucleotide) is correlated with the progression of MS. These statements in Example 7 also do not address the distinct concept of a deletion of both nucleotides 1580 and 1581, as is required by claims 7 and 19-21. Note that the specification has not established that the findings obtained with a deletion of nucleotide 1580 can be extrapolated to findings obtained with a deletion of both nucleotides 1580 and 1581.

Regarding the fact that the findings reported in Figure 6 are not statistically significant (i.e., the p value for individuals homozygous for the deletion versus homozygous for the absence of the deletion was reported as 0.059, and the p value for individuals homozygous for the deletion versus individuals having one allele with a TG was reported as 0.177), the response states that the higher p value was due to the low sample numbers available for the del/del group. It is stated that "In the log-rank test that considered all three genotypes, the p value is smaller than all pair-wise comparison. This can occur only if the del/del vs TG/del, del/del vs TG/TG and the TG/del vs TG/TG shown the same trends. For this reason, one can conclude that both del/del (homozygous) and del/TG (heterozygous) genotypes are protective (i.e., correlated with a lesser likelihood of rapid progression of MS). " However, Applicants do not provide

any evidence to support this assertion. As set forth in MPEP 716, the arguments of counsel cannot take the place of evidence in the record. In re Schulze,346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965).

The response further states that "additional studies can and have been carried out in this case, using the methods described in the application, and that the subsequent studies using the described methods would be routine rather than undue. These subsequent studies have already provided confirmation of the inventors initial results by way of Wang et al., referenced by the Examiner. Wang et al. expanded upon the initial study by using a larger population of individuals to support their results, and also proposed a mechanism through which the deletions could slow progression of MS by modulating CD24 mRNA stability."

These arguments have been fully considered but are not persuasive. Applicants do not provide any evidence to support a conclusion that further studies can and have been carried out to confirm the inventors findings. Regarding the Wang et al references, these references are co-authored by the present inventors and thereby are not impartial in nature. As set forth in MPEP 716.02, "The reason for requiring evidence in declaration or affidavit form is to obtain the assurances that any statements or representations made are correct, as provided by 35 U.S.C. 25 and 18 U.S.C. 1001." Permitting a publication to substitute for expert testimony would circumvent the guarantees built into the statute. Ex parte Gray, 10 USPQ2d 1922, 1928 (Bd. Pat. App. & Inter. 1989). " Note, this should not be construed as an invitation for providing additional declarations or affidavits. As further stated in the MPEP 716.01 regarding the

timely submission of evidence:

A) Timeliness.
Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:
(1) prior to a final rejection,
(2) before appeal in an application not having a final rejection, or
(3) after final rejection and submitted
(i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or
(ii) with a satisfactory showing under 37 CFR 1.116(b) or 37 CFR 1.195, or
(iii) under 37 CFR 1.129(a).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634